REMARKS

Claims 1-21 are pending. Claims 1-3 and 14 have been amended.

In particular, claim 1 has been amended to specify a method of selectively reducing the number or activity of macrophages "within a localized area of tissue" by "contacting the area of tissue" with the macrophage-binding compound. Support for the amendment of claim 1 can be found in throughout the specification and the claims as filed.

Claims 1 and 2 have also been amended to specify that the recited compound comprises a first and second agent. Support for the amendment of claims 1 and 2 can be found throughout the specification and the claims as filed.

Claim 2 has been amended to remove reference to disease prevention.

Claim 3 has been amended to depend solely from claim 2.

Claim 14 has been amended to correct a typographical error.

The claim amendments made herein are solely for the purpose of expediting prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in this or in any former Office Action issued in the parent application. Applicant reserves the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another subsequent application. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the claims by the amendments requested herein entitled "VERSION WITH MARKINGS TO SHOW CHANGES MADE". For the Examiner's convenience, a copy of the pending claims is also attached as Appendix A.

Rejection of Claims 2-6, 8-12, and 19-21 Under 35 U.S.C. § 112, First Paragraph

Although the Examiner agrees with Applicant that the specification is enabling for the treatment of macrophage related disorders, the Examiner maintains the rejection of claims 2-6, 8-12, and 19-21 under 35 U.S.C. §112, first paragraph, as not being enabled for the prevention of such disorders. Specifically, the Examiner states that "without a known cause for a disease, prevention of said disease is not enabled." The Examiner further states that the Applicant does not show a nexus between the data

provided for chronic skin disease and other diseases caused by aberrant macrophage activity and/or numbers. Based on this, the Examiner concludes that "since the cause of psoriasis is not known . . . it is not clear how a nexus can be formed."

Applicant respectfully traverses the rejection. However, to expedite prosecution, claim 2 has been amended to remove reference to "prevention" of a disease in a subject characterized by aberrant activity or numbers of macrophages within a selected area of the subject." Accordingly, based on the forgoing amendments, it is respectfully requested that the rejection be withdrawn.

Rejection of Claims 1-6 Under 35 U.S.C. § 102(a)

The Examiner maintains the rejection of claims 1-6 under 35 U.S.C. §102 (a) as being anticipated by Curnow, R. (*Cancer Immunol. Immunother.* 45:210-215 (1997)) as evidenced by Graziano *et al.* (*J. Immunol.* 155:4996-5002 (1995)). In particular, the Examiner alleges that Curnow teaches that "down modulating CD64 by CD64 specific antibodies reduces the activity of CD64 bearing cells such as macrophages" and that the agent disclosed by Graziano has the function of the claimed invention.

Applicant respectfully traverses this rejection. As amended, claims 1-6 are drawn to a method of selectively reducing the number or activity of macrophages (*e.g.*, as a method of treatment) within a localized area of tissue using two different agents, *i.e.*, a first agent which binds to an Fc receptor and a second agent which kills or reduces the activity of the macrophages. Curnow fails to teach or suggest any such method which requires two separate and distinct agent. Indeed, Curnow merely describes a single agent, *i.e.*, mAbH22 (i.e., MDX-33), which binds to circulating monocytes.

Moreover, Curnow fails to teach or suggest the claimed step of localized administration of a macrophage-binding compound, as encompassed by claims 1-6.

Based on at least the foregoing, it is respectfully requested that the rejection under 35 U.S.C. § 102(a) be reconsidered and withdrawn.

Rejection of Claims 1-6 and 18 Under 35 U.S.C. § 102(b)

The Examiner also maintains the rejection of claims 1-6 and 18 under 35 U.S.C. §102 (b) as being anticipated by Ericson *et al.* (*British Journal of Haematology*, 92:718-724 (1996)). The Examiner states that Ericson *et al.* teach a monoclonal antibody that can bind and down modulate FcγRI receptor on circulating monocytes, e.g., in ITP patients, and thus, which has the function of the agents recited in the present claims.

Applicant respectfully traverses this rejection. As pointed out above, the claims as amended are drawn to methods which use a composition made up of two separate and distinct agents. Like Curnow, Ericson *et al.* fail to teach or suggest using two separate agents as defined in the pending claims. Ericson *et al.* only teach administration of a single mAb.

Moreover, like Curnow, Ericson *et al.* fail to teach or suggest reducing the number or activity of macrophages by local administration (*e.g.*, by "contacting an area of tissue") with a macrophage-binding compound as encompassed by the pending claims.

Based on at least the foregoing, it is respectfully requested that the rejection under 35 U.S.C. § 102 (a) be reconsidered and withdrawn.

Rejection of Claims 1-2, 8-12, and 21 Under 35 U.S.C. § 103(a)

The Examiner maintains the rejection of claims 1-2, 8-12, and 21 under 35 U.S.C. §103(a) as being unpatentable over Curnow, R.T. (cited *supra*), Graziano *et al.* (cited *supra*), Ericson *et al.* (cited *supra*), Uhr *et al.* (USPN 5,686,072), Ghetie *et al.* (USPN 5,578,706), Rybak *et al.* (USPN 5,840,840), Pastan (USPN 5,489,525), and Bjerke *et al.* (ACTA Derm. Venereol. (Stockh) Suppl. 186:141-142 (1994)).

In particular, the Examiner states that the cited references "are not limited to monocytes but also include macrophages . . . and that the circulatory system contains connective tissue." The Examiner further points out that "the instant claims do not recite 'within a localized area of tissue.'"

Applicant respectfully traverses this rejection. However, to expedite prosecution, the claims have been amended to specify that the recited macrophage-binding compound is administered locally (*e.g.*, by contacting an area of tissue). Accordingly, the claims are drawn to methods which target the aberrant activity and/or numbers of macrophages

within a localized area of tissue, not freely circulating monocytes as taught in the prior art. None of the cited references, either alone or in combination, teach or suggest the treatment of such macrophage-mediated disorders which exist within a localized area of tissue as opposed to in the circulatory system, let alone in the manner taught by Applicant.

Based on at least the foregoing, it would not have been obvious to have combined the individual teachings of these references to have arrived at the claimed invention. Accordingly, based at least on the foregoing, it is respectfully requested that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Rejection of Claims 1 and 13-17 Under 35 U.S.C. §103 (a)

The Examiner maintains the rejection of claims 1 and 13-17 under 35 U.S.C. §103(a) as being unpatentable over Curnow, R.T. (cited supra), Graziano *et al.* (cited supra), Ericson *et al.* (cited supra), in view of McGrath *et al.* (USPN 5,580,715), Estis *et al.* (USPN 5,026,557), Rodwell *et al.* (USPN 4,671,958), Lifson *et al.* (USPN 4,869,903), and Bagshawe (USPN 5,658,568). In particular, the Examiner states that, in combination, the newly cited references of McGrath, Estis, Rodwell, Lifson, and Bagshawe disclose the targeting of macrophages with a immunotoxin and a liposome using, for example, an antibody or antibody fragment that binds to FcγRI as taught by Curnow, Graziano, and Ericson *et al.* Thus, based on the combination of these eight (8) references, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to have arrived at the claimed invention.

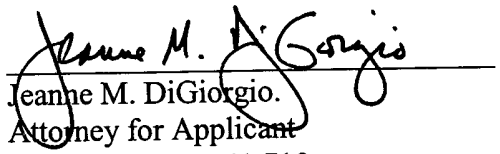
Applicant respectfully traverses this rejection. As described above, the content of which is reiterated here, the claims are drawn to methods which target the aberrant activity and/or numbers of macrophages within a localized area of tissue, not the freely circulating monocytes as taught in the prior art. None of the cited references, either alone or in combination, teach or suggest the treatment of such macrophage-mediated disorders which exist within a localized area of tissue as opposed to in the circulatory system, let alone in the manner taught by Applicant.

Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. §103(a), be withdrawn.

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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Attachment: Appendix A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Claims 1-3 and 14 have been amended as follows.

1. (Amended) A method of selectively reducing the number or activity of macrophages within a localized area of tissue, comprising contacting the area of tissue ~~macrophages~~ with a macrophage-binding compound comprising (a) ~~an~~ a first agent which binds to an Fc receptor at a site which is distinct from that bound by endogenous immunoglobulins ~~to~~; and (b) ~~an~~ a second agent which kills or reduces the activity of the macrophages.

2. (Amended) A method of treating ~~or preventing~~ a disease in a subject characterized by aberrant activity or ~~number~~ numbers of macrophages within a selected area of the subject, comprising locally administering to the area a macrophage-binding compound comprising (a) ~~an~~ a first agent which binds to an Fc receptor; and (b) ~~an~~ a second agent which kills or reduces the activity of the macrophages.

3. (Amended) The method of ~~either of claims 1 or~~ claim 2, wherein the agent which binds to an Fc receptor binds at a site which is not bound by an endogenous immunoglobulin.

14. (Amended) The method of claim 13, wherein the agent which kills or reduces the activity of a macrophage is dichoromethylene diphosphonate (CL2MDP) or ~~derivatives~~ a derivative thereof.

Appendix A

Pending Claims

1. (Amended) A method of selectively reducing the number or activity of macrophages within a localized area of tissue, comprising contacting the area of tissue with a macrophage-binding compound comprising (a) a first agent which binds to an Fc receptor at a site which is distinct from that bound by endogenous immunoglobulins; and (b) a second agent which kills or reduces the activity of the macrophages.

2. A method of treating a disease in a subject characterized by aberrant activity or numbers of macrophages within a selected area of the subject, comprising locally administering to the area a macrophage-binding compound comprising (a) a first agent which binds to an Fc receptor; and (b) a second agent which kills or reduces the activity of the macrophages.

3. The method of claim 2, wherein the agent which binds to an Fc receptor binds at a site which is not bound by an endogenous immunoglobulin.

4. The method of either of claims 1 or 2, wherein the Fc receptor is an Fcγ receptor (FcγR) or an Fcα receptor (FcαR).

5. The method of claim 4, wherein the Fcγ receptor is selected from the group consisting of FcγRI, FcγRII and FcγRIII.

6. The method of claim 5, wherein the Fcγ receptor is a human FcγRI.

7. The method of claim 4, wherein the Fc receptor is a human FcαR.

8. The method of either of claims 1 or 2, wherein the macrophage-binding compound comprises an anti-Fc receptor antibody conjugated to a toxin.

9. The method of claim 8, wherein the anti-Fc receptor antibody is an anti-Fcγ receptor antibody or a fragment thereof.

10. The method of claim 9, wherein the anti-Fcγ receptor antibody is a monoclonal antibody selected from the group consisting of mab 22, 32 and 197, or a fragment thereof.

11. The method of claim 9, wherein the anti-Fcγ receptor antibody is a humanized antibody H22 produced by the cell line having ATCC accession number CRL 1117 or a fragment thereof.

12. The method of claim 8, wherein the toxin is selected from the group consisting of Gelonin, Saporin, Exotoxin A, Onconase and Ricin A.

13. The method of claim 1, wherein the agent which kills or reduces the activity of the macrophages is encapsulated within a liposome.

14. The method of claim 13, wherein the agent which kills or reduces the activity of a macrophage is dichoromethylene diphosphonate (CL2MDP) or a derivative thereof.

15. The method of claim 13, wherein the agent which binds to an Fc receptor is a single chain antibody.

16. The method of claim 13, wherein the agent which binds to an Fc receptor is an anti-Fcγ receptor antibody or a fragment thereof.

17. The method of claim 13, wherein the agent which binds to an Fc receptor is a single chain anti-Fcγ receptor antibody or a fragment thereof.

18. The method of claim 1, wherein the contacting step occurs in culture.

19. The method of either of claims 1 or 2, wherein the macrophage-binding compound is administered topically, intradermally or subcutaneously in a pharmaceutically acceptable carrier.

20. The method of claim 2, wherein the disease is characterized by enhanced proliferation and/or growth factor secretion of the macrophage.

21. The method of claim 2, wherein the disease is selected from the group consisting of psoriasis, atopic dermatitis, scleroderma, cutaneous lupus erythematosis, Human Immunodeficiency Virus infection, multiple sclerosis, rheumatoid arthritis, Chronic Polymorphic Light Dermatosis, Chronic Obstructive Pulmonary Diseases, and Wegener's Granulomatosis.